World Health Organization

Rapid Communication:

Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis

(MDR/RR-TB)

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Rapid Communication:

Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)

Background

Providing evidence-based guidelines to inform public health service delivery for Member States and other stakeholders is one of the core responsibilities of the World Health Organization (WHO).

The most recent WHO evidence-based guidelines for the treatment of multidrug-resistant[i] or rifampicin-resistant tuberculosis (MDR/RR-TB) were published in October 2016. Subsequently, new evidence prompted a public call for data by WHO in anticipation of a formal review. Anonymized individual data received from clinical trials, cohort/observational studies and programmatic implementation of both longer and shorter MDR-TB regimens were incorporated into an individual MDR/RR-TB patient data base (IPD) hosted by McGill University, Canada, under contract with WHO.

Cochrane international methods for meta-analysis were followed to assess the relative contributions of individual medicines to patient treatment outcomes and to inform the design of MDR/RR-TB treatment regimens, the duration of treatment and the impact of drug resistance profiles on those outcomes.

WHO convened a Guideline Development Group meeting on 16-20 July 2018 to assess the results of these analyses using the international GRADE system (Grading of Recommendations, Assessment, Development and Evaluation for scientific evidence assessment and development of evidence-based policy guidelines and recommendations. The new MDR-TB treatment guidelines will be released later in 2018. These guidelines will replace all previous and current WHO guidelines on treatment of MDR/RR-TB.

This Rapid Communication aims to inform TB programme managers and other stakeholders of WHO Member States about the key implications for MDR-TB treatment regimens arising from the new evidence assessment. It highlights the immediate steps to be taken to ensure that MDR/RR-TB patients receive treatment in accordance with the latest evidence on effectiveness and safety.

While understanding that it would not be immediately possible to achieve the new standards of care in every individual MDR-TB patient, strategic planning should start immediately to enable rapid transition to the upcoming new WHO guidelines.

Data sources

- An IPD database with over 12,000 patient records from 50 studies of longer MDR-TB regimens;
- New data from 26 countries following the WHO public call, including the use of the shorter regimen in African and Asian settings and the use of bedaquiline worldwide;
- Aggregated results from the Otsuka phase III randomised controlled trial of delamanid, released in October 2017 and initially assessed by WHO in an expedited review in January 2018;

[i] Combined resistance to rifampicin and isoniazid, the two most important anti-TB drugs.

- Aggregated final results from the STREAM Stage 1 randomised controlled trial of a 9-month shorter MDR-TB regimen, after release of the interim results in October 2017 and initial assessment by WHO in an expedited review in February 2018.
- Pharmacokinetic and safety data from trials of bedaquiline and delamanid in children to consider the extension of treatment recommendations to children and adolescents.

Final results (outcomes) of treatment were used for developing policy recommendations. Patient data series that only reported interim results (such as 6-month culture conversion) were not considered, given that correlation between such surrogate endpoints and final outcomes (such as cure or treatment failure) has not been reliably established.

Treatment principles

- **Ahead of enrolment on MDR-TB treatment, all patients should receive appropriate counselling to enable informed and participatory decision-making.**
- **Patient information material needs to reflect the new changes so that patients are appropriately informed about their treatment options.**
- **Social support to enable adherence to treatment is very important to ensure a patient-centred approach to the delivery of care.**
- **Active TB drug safety monitoring and management (aDSM) is essential for all patients enrolled on MDR-TB treatment.**

Key medicine changes

Longer MDR-TB regimens[ii]

The revised grouping of TB medicines recommended for use in longer MDR-TB regimens is presented in Table 1. Medicines have been regrouped into **three categories and ranked** based on the latest evidence about the balance of effectiveness to safety:

- **Group A**: Medicines to be prioritised: levofloxacin/moxifloxacin, bedaquiline and linezolid
- **Group B**: Medicines to be added next: clofazimine, cycloserine/terizidone
- **Group C**: Medicines to be included to complete the regimens and when agents from Groups A and B cannot be used: ethambutol, delamanid[iii], pyrazinamide, imipenem-cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid;

Medicines no longer recommended are kanamycin and capreomycin, given increased risk of treatment failure and relapse associated with their use in longer MDR-TB regimens. Use of amikacin did not show a

[ii] Longer MDR-TB regimens usually last 18-20 months and may be standardized or individualized. These regimens are usually designed to include at least five medicines considered to be effective.

[iii] The position of delamanid will be re-assessed once individual patient data from Otsuka trial 213 has been reviewed; these data were not available for the evidence assessment outlined above.

similar association, although the same safety concerns as for the other injectables apply. Amoxicillin-clavulanic acid is only to be used to accompany the carbapenems.

Table 1 also indicates the overall approach to designing longer MDR-TB regimens for adults and children based on the revised grouping. The regimen is designed by adding medicines sequentially going down the three groups.

Apart from the ranking by balance of effectiveness and harms, choice is also determined by: a preference for oral over injectable agents; the results of drug-susceptibility testing (DST); the reliability of existing DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug-drug interactions.

Consultation on how best to optimise these aspects of MDR-TB treatment is ongoing. This includes the minimum number of medicines required in designing MDR-TB regimens based on the revised grouping, while maximising regimen efficacy in the presence of resistance to or tolerability of individual agents.

Options for the choice of agents for the intensive and continuation phases, more detailed guidance on patient selection criteria, number of medicines and duration of treatment, adult and paediatric dosing, treatment of extensively drug resistant disease (XDR-TB), and the use of DST results will be provided at the time of release of the final WHO guidelines.

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

1. Evidence on the safety and effectiveness of Bdq beyond 6 months was insufficient for review; extended Bdq use in individual patients will need to follow 'off-label' use best practices.
2. Optimal duration of use of Lzd is not established. Use for at least 6 months was shown to be highly effective, although toxicity may limit its use.

3. The position of Dlm will be re-assessed once individual patient data from trial 213 has been reviewed; these data were not available for the evidence assessment in July outlined above. Evidence on the safety and effectiveness of Dlm beyond 6 months was insufficient for review; extended use of Dlm in individual patients will need to follow 'off-label' use best practices.
4. Evidence on concurrent use of Bdq and Dlm was insufficient for review.
5. Z is only counted as an effective agent when DST results confirm susceptibility.
6. Amoxicillin-Clavulanic acid is administered with every dose of Imp-Cln or Mpm but is not counted as a separate agent and should not be used as a separate agent.
7. Am and S are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used and if DST results confirm susceptibility (S resistance is not detectable with 2nd line molecular line probe assays and phenotypic DST is required).

Shorter MDR-TB regimen[iv]

- The STREAM Stage 1 trial showed that, in eligible patients, treatment success was similar between patients receiving a shorter MDR-TB regimen and longer regimens conforming to prior WHO recommendations.
- In observational studies, shorter MDR-TB regimens similar to the one studied in the STREAM Stage 1 trial showed an overall comparable likelihood of treatment success with longer regimens, with a lower risk of treatment interruption. However, shorter regimens were associated with higher risk of treatment failure and relapse compared to longer regimens, especially when resistance to key medicines in the shorter regimen was present or when longer regimens included one or more of the Group A medicines listed above in Table 1.
- Evidence is lacking for the performance of shorter MDR-TB regimens modified from the standardized form recommended in 2016 (e.g. bedaquiline or linezolid replacing the injectable agent or levofloxacin replacing moxifloxacin).

Choice of a MDR-TB regimen

- Treatment options for MDR-TB are increasingly becoming more individualised as a result of innovations in diagnostics and growing scientific understanding of the molecular basis for drug resistance and the pharmacokinetics and pharmacodynamics of TB medicines. Three signals are clear from the current scientific evidence assessment:
  - The feasibility of effective and **fully oral treatment regimens** for most patients;
  - The need to ensure that **drug resistance is excluded** (at least to the fluoroquinolones and injectables) before starting patients on treatment, especially for the shorter MDR-TB regimen;
  - The need for **close monitoring** of patient safety and treatment response and **a low threshold for switching non-responding patients or those experiencing drug intolerance** to alternative medicines and/or new regimens based on the regrouping of agents in Table 1.

[iv] In this document a **shorter MDR-TB regimen** refers to a course of treatment for MDR/RR-TB lasting 9 to 12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings. The usual structure is as follows: 4-6 Km(Am)-Mfx-Pto(Eto)-Cfz-Z-Hhigh-dose-E/5 Mfx-Cfz-Z-E

- Programmes and their stakeholders should start transitioning towards implementation of the upcoming new WHO guidelines at the earliest opportunity;
- Programmes and their stakeholders using longer MDR-TB regimens with good results and with adequate capacity for monitoring drug safety should:
  - assess and adjust treatment of individual patients on treatment without waiting for existing stocks of medicines - most notably the injectables - to be used up;
  - in the interim, inform patients on treatment about the relative benefits and harms of continuing their current regimens, most notably the injectables and ethionamide-protionamide;
  - intensify clinical, safety and microbiological monitoring in order to rapidly switch patients to new longer MDR-TB regimens upon the first signs of non-response or drug intolerance.
- Programmes and their stakeholders using the standardized shorter MDR-TB regimen with good results and with adequate capacity for monitoring drug safety (especially ototoxicity) should:
  - replace kanamycin with amikacin in the shorter regimen, without waiting for existing stocks of kanamycin to be used up;
  - in the interim, inform patients on treatment about the relative benefits and harms of continuing the shorter regimen with kanamycin;
  - intensify clinical, safety and microbiological monitoring in order to rapidly switch patients to new longer MDR-TB regimens upon first signs of non-response, ototoxicity or drug intolerance.
- Decisions to start newly diagnosed patients on the standardized shorter MDR-TB regimen should be made according to patient preference and clinical judgement, for patients who do not have any of the following conditions:
  - Resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance);
  - Exposure to one or more 2nd line medicines in the regimen for >1 month (unless susceptibility these 2nd line medicines is confirmed);
  - Intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions);
  - Pregnancy;
  - Disseminated, meningeal or central nervous system TB; or any extrapulmonary disease in HIV patients.
- Programmes and their stakeholders considering the use of modified shorter regimens should note that evidence is currently lacking on the effect of replacing any of the agents with alternatives in the shorter regimen (e.g replacing the injectable with bedaquiline or other oral agents; replacing moxifloxacin with levofloxacin).
- Programmes and their stakeholders are advised to consider any variations to the standardized shorter MDR-TB regimen only under operational research conditions, following these steps:
  - Preparation of a suitable protocol identifying the eligibility criteria, regimen composition, monitoring schedules and other key elements (see here for a generic template);
  - Approval by a national ethics review committee, ahead of any patient enrolment;

  - Treatment delivery under WHO-recommended standards, including informed consent; principles of good clinical practice; aDSM; and regular patient monitoring to assess regimen effectiveness.

- Programmes and their stakeholders are welcome to solicit advice from WHO before they mount operational research for modified shorter regimens.

Next steps

- Consolidated, updated and more detailed WHO policy guidelines on MDR-TB treatment will be provided by the end of 2018, including the detailed GRADE evidence assessment underpinning the changes according to the requirements of the WHO Guidelines Review Committee.
- The 2018 WHO policy guidelines will be accompanied by an update of the *Companion Handbook to WHO guidelines for the programmatic management of drug-resistant tuberculosis;*
- WHO is establishing a multi-stakeholder Task Force[v] to coordinate the support to national TB programmes in their rapid transition to the key changes envisaged. As a first priority, the Task Force will support countries to undertake a rapid situational assessment of their most urgent needs and adjust their medicine and diagnostics procurement plans. Subsequent activities will involve support to countries to update their national guidelines, future programme budgets and monitoring systems to enable the switch to more effective MDR-TB regimens. Draft terms of reference for the Task Force are outlined in Annex 1.

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[v] Already represented: WHO; USAID; The Global Fund to Fight AIDS, TB and Malaria; the Stop TB Partnership; the Global Drug Facility; Unitaid (other members to be finalised during August 2018).

WHO Task Force to support country transition towards new recommendations for the treatment of MDR-TB

Background

WHO will be releasing new recommendations for the treatment of multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) later this year. These recommendations will have major implications for national TB programmes, their technical and funding partners, and other stakeholders.

Implementation of the new recommendations should happen quickly given landmark changes to the treatment of MDR/RR-TB; nevertheless, it will be important to minimise disruptions to national health systems while ensuring that patient diagnosis and treatment continues to increase and improve.

WHO is thus creating a multi-partner Task Force to assist high MDR-TB burden countries and other Member States to prepare for a smooth transition towards the implementation of the new recommendations.

Membership to the Task Force is by self-nomination to WHO at LDR@who.int and open to any person or agency with expertise, capacity and resources to support countries during the transition phase and towards full implementation of the new WHO guidelines. Please specify your expertise and experience when responding.

Expertise and experience sought

Diagnostics and laboratory strengthening; procurement and supply chain management; budget planning; active drug safety monitoring and management; country-based technical support; clinical patient management; training; advocacy & social mobilisation.

Objectives

- To assess and provide solutions to the short-term and longer-term operational implications of the new WHO recommendations on national MDR-TB guidelines, training of key staff, funding, targets, and adjustment of short and longer-term procurement plans;
- To work together to assess country-specific challenges and provide solutions, especially during the transition phase, and to ensure that the transition is followed up by support to countries for full implementation of the new guidelines;
- To maintain active and clear communication between all major stakeholders on the actions undertaken to support transition

Deliverables

- Advice and support to countries on the content and process for transition plans towards full implementation of the new guidelines;
- Advice to WHO on further actions and additional support aids to enable full implementation.

Timeline

It is expected that the work of the Task Force will start in August 2018, with objectives accomplished by June 2019 and reported to the WHO Strategic & Technical Advisory Group for TB (WHO-STAG).